

## Hyperuricemia as a potential risk factor for type 2 diabetes and diabetic nephropathy

Hiperuricemia como potencial fator de risco para diabetes tipo 2 e nefropatia diabética

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Serum uric acid has recently received attention as a potential biomarker independently predicting the development of hypertension, *diabetes mellitus*, and chronic kidney disease.<sup>1-3</sup> Elevated serum uric acid has also been reported to predict development of nephropathy in type 1 diabetes.<sup>4-7</sup> Less is known, however, about the role of serum uric acid in predicting nephropathy in type 2 diabetes.

In this issue of the Brazilian Journal of Nephrology, Fouad *et al.*<sup>8</sup> performed a case-control study in Egyptian adults with and without type 2 diabetes that were matched for age, sex and body mass index (BMI). The study included 986 participants; 250 non-diabetic controls, 352 with type 2 diabetes for less than 5-years and 384 with type 2 diabetes for more than 5-years.

The participants of the three groups were similarly obese with mean BMI between 30 and 32 kg/m<sup>2</sup>. The most important observation was that serum uric acid showed a stepwise increase between groups, and overall 32% of subjects with type 2 diabetes demonstrated hyperuricemia (defined as serum uric acid > 7.0 mg/dl). Furthermore, the increase in serum uric acid correlated with worsening hypertension, albuminuria and kidney function.

The paper is interesting for several reasons. First, some studies of *diabetes mellitus* have reported serum uric acid to be lower than what is observed in nondiabetic subjects, and this has been attributed to elevated GFR (hyperfiltration) and poor glycemic control (elevated HbA1c).<sup>9,10</sup> Bo *et al.*<sup>11</sup>, however, noted that subjects with

type 2 diabetes with kidney disease tended to have higher serum uric acid levels.

In the study by Fouad *et al.*<sup>8</sup> the serum uric acid was higher in subjects with type 2 diabetes, with the highest levels of serum uric acid observed in those with poor glycemic control. One potential explanation provided by the authors was that their subjects already had kidney disease with falling eGFR, for which reason hyperfiltration that is commonly seen early in the course of diabetic kidney disease was not observed.

This may relate to the fact that in type 2 diabetes subjects often have other comorbidities including hypertension and/or vascular disease that may lead to earlier development of kidney disease than is normally observed during the initial years of type 1 diabetes. It is also possible that other risk factors may be playing an important role in causing early kidney disease in this population. One recently proposed risk factor is heat stress and dehydration, that may be more common among individuals living in hot environments.<sup>12</sup>

There are some limitations of the study worth mentioning. First, it is unclear if the elevated serum uric acid in subjects with type 2 diabetes simply reflects worse renal function among this group. It would have been interesting to determine if serum uric acid was elevated independently of the eGFR in subjects with type 2 diabetes.

Second, the study was cross-sectional, and hence it is not possible to determine causality, i.e. if elevated serum uric acid mediated the the development of nephropathy. Nevertheless, the observation

Submitted on: 09/06/2016.  
 Approved on: 09/10/2016.

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DOI: 10.5935/0101-2800.20160061

that hyperuricemia was common in subjects with type 2 diabetes compared to non-diabetic control subjects with similar levels of obesity is fascinating, as is the stepwise increase in serum uric acid with duration of diabetes.

We have much more to learn about the role of uric acid in *diabetes mellitus* and diabetic kidney disease. Some early pilot studies suggest lowering serum uric acid can improve insulin resistance in subjects with heart failure or metabolic syndrome.<sup>13,14</sup> Other small studies suggest lowering serum uric acid may improve diabetic nephropathy.<sup>15</sup>

It is also interesting that the potential benefit of lowering serum uric acid may be primarily in subjects who are not taking agents that block the renin angiotensin system. For example, one Egyptian study reported marked exacerbation of nondiabetic kidney disease when serum uric acid lowering agents were withdrawn, but only in those not taking ACE inhibitors.<sup>16</sup> Currently there is a large clinical trial ongoing in the North America to determine if lowering serum uric acid can halt or delay the development of nephropathy in subjects with type 1 diabetes.<sup>17</sup>

It would seem important to design a similar study in subjects with type 2 diabetes. In the meantime, given the potential toxicities of allopurinol, we do not recommend routine lowering of serum uric acid in patients with type 2 diabetes, but would reserve such treatment for those with gout, uric acid stones, or those with marked hyperuricemia (serum uric acid > 9.0 mg/dl).

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